REMARKS

Reconsideration of the application is respectfully requested.

Claims 1, 5, 6 and 55 are in the application.

Claims 1, 5, 6 and 55 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Grahnen et al. (Eur. J. Biochem., 80, 573-580 (1997)) in view of Spring et al. (U.S. Patent No. 5,643,721) further in view of Degen et al. (U.S. Patent No. 5,567,615). The Examiner admitted that "Grahnen et al. fail to teach the ligand attached to the support via an epoxy linkage." To overcome this deficiency, the Examiner asserted that Spring et al. teach ligands attached to an agarose substrate by an epoxy linker. Further, the Examiner asserted that Degen et al. teach a ligand having a hydroxyl group attached to a polymer support via an epoxy linker. The Examiner concluded:

> Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the apparatus of Grahnen et al., an epoxy linkage between the ligand and the agarose support as taught by Spring et al., in order to provide a simple method of attaching ligands having a hydroxyl group to a substrate by way of a spontaneous covalent attachment as taught by Degen et al. Degen et al. do not specifically teach a bromosulphophthalein ligand being attached to an agarose support. However, Degen et al. teach that epoxy linker attachment is advantageous for ligands having a hydroxyl group and Spring et al. teach that an epoxy linker is advantageous to link ligands to an agarose support. Since bromosulphophthalein comprises a hydroxyl group, Degen et al. teach the epoxy linkage would be a simpler and advantageous method of attachment of bromosulphophthalein to a substrate, and Spring et al. teach that it would have been obvious for the substrate that the epoxy linker attaches to, to be an agarose support. Therefore an epoxy linker is advantageously used to attach the ligand to the agarose substrate of Grahnen et al.

The Examiner's assertions are respectfully traversed.

As noted by the Examiner, Grahnen et al. do not use an epoxy linker to attach bromosulphophthalein (BSP) to an insoluble support. Rather, Grahnen et al. relies on sodium borohydride, presumably acting as a reducing agent, to cause the BSP to link to the support. (P.

754, bottom of left column). It is noted that Grahnen et al. uses BSP for extracting porcine ligandin from porcine liver cytosol. (See, Abstract at p. 573 of Grahnen et al.).

In Applicants' last response, it was argued that the binding characteristics of BSP are unpredictable. At pp. 4-5 of the Official Action, the Examiner responded to the previous arguments as follows,

> Applicant's argument is not persuasive because at pages 579-580 Grahnen et al. discuss that the increased specific activity may be due to differences in isolation methods. Nowhere does Grahnen et al. describe that a linker between the BSP and the support affects the binding characteristics of BSP. The passage describing the alterable binding characteristics of BSP at pages 579-580 of Grahnen et al. is therefore not relevant to the affect of a linker on the binding characteristics of BSP. Furthermore, Grahnen et al. do not teach away from using a linker to attach BSP to the support. Therefore one having ordinary skill would expect BSP to retain its binding characteristics and would have been motivated to utilizing an epoxy linker between the BSP and the sepharose support as described above. One having ordinary skill would also have a reasonable expectation of success in using the epoxy linker with BSP since the prior art teaches an epoxy group linked to a hydroxyl group on a ligand and the BSP ligand contains a hydroxyl group.

The Examiner's assertions are respectfully traversed.

As admitted by the Examiner, at pp. 579-580 of Grahnen et al., it is noted that increased specific activity may be due to "differences in isolation methods." The Examiner further indicated, as quoted above, that Grahnen et al. does not "describe that a linker between the BSP and the support affects the binding characteristics of BSP." The Examiner concluded that the "passage describing the alterable binding characteristics of BSP" is "therefore not relevant to the affect of a linker on the binding characteristics of BSP."

Grahnen et al. is directed to a method for the purification of porcine ligandin. One skilled in the art understands Grahnen et al. to be for the stated purpose. Thus, one skilled in the art would take Grahnen et al., with the associated use of sodium borohydride for causing BSP to link to a support, for purifying porcine ligandin. Grahnen et al. is not directed to the use of multiple

linkers for linking BSP to a support. Rather, a very specific methodology is disclosed in Grahnen et al. to achieve purification of porcine ligandin.

Moreover, as admitted by the Examiner, Grahnen et al. acknowledges that the functionality of extracting porcine ligandin is affected by "differences in the isolation methods". Thus, one skilled in the art reading Grahnen et al. in its entirety, would understand that changes in the methodology of preparing the BSP will affect the purification ability of a resulting device.

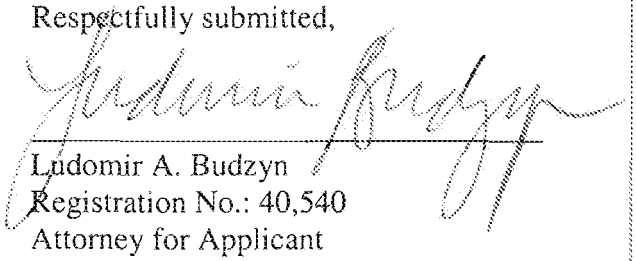
It is the Examiner's position that Grahnen et al. does not state that a linker has any affect on the binding characteristics of BSP. In response, the isolation methods referred to by Grahnen et al. contain not only the method of purifying porcine ligandin, but also the preparation of the BSP for such purification. Subsumed within this method of preparation is the use of sodium borohydride, rather than epoxy linkers. The isolation method of Grahnen et al. is based explicitly on the use of sodium borohydride. As stated at p. 580 of Grahnen et al., it is noted that "differences in the isolation methods" provide diversity in results. The use of sodium borohydride results in a different chemical linkage than with the use of epoxy linkers. BSP linked with sodium borohydride is configured differently than if linked with an epoxy. As stated at p. 580 of Grahnen et al., a "poor correlation" has been noted between the binding of BSP with certain protein. This unpredictability discourages one from altering the preparation method of Grahnen et al.

Grahnen et al. is directed to a specific isolation method which includes a specific process of preparing BSP using a sodium borohydride linker. Grahnen et al. acknowledges unpredictability of BSP due to isolation methods. These isolation methods include the linking of BSP to a support with sodium borohydride. Any changes from this methodology results in unpredictable results. As set forth at MPEP §2143.01(III), "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been ***predictable*** to one of ordinary skill in the art." It is respectfully submitted that Grahnen et al. can not be modified to use an epoxy linker as suggested by the Examiner.

Accordingly, it is respectfully submitted that claim 1, along with dependent claims 5, 6 and 55, are patentable over Grahnen et al., Spring et al., and Degen et al., each taken alone or in combination.

Favorable action is earnestly solicited. If there are any questions or if additional information is required, the Examiner is respectfully requested to contact Applicant's attorney at the number listed below.

Respectfully submitted,



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